CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20738/S001

ADMINISTRATIVE DOCUMENTS

OCT 28 1998

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RHPM Review of Labeling

NDA: 20-738/SE2-001 Teveten (eprosartan mesylate) Tablets

Date of submission: October 2, 1998 (AF)

Date of receipt: October 5, 1998

Applicant: SmithKline Beecham

Background: We issued an approvable letter on September 23, 1998, for NDA 20-738/S-001, that provided for draft labeling revised under **DOSAGE AND ADMINISTRATION**, **CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects** and **Clinical Trials**, **PRECAUTIONS, Geriatric Use**, and **ADVERSE REACTIONS, Laboratory Test Findings**. The letter requested final printed labeling identical in content to an enclosed marked-up draft.

Review: The submitted final printed labeling has been revised as follows:

CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects: In the second paragraph, third sentence, "once- or" has been added. The sentence now begins, "Blood pressure control is maintained with once- or twice-daily dosing..."

CLINICAL PHARMACOLOGY, Clinical Trials: The second and third paragraphs have been revised to read as follows (additions underlined, deletions struck through):

The fourth paragraph has been revised to read as follows:

> "Peak (1 to 3 hours) effects were uniformly, but moderately, larger than trough effects with b.i.d. dosing, with the trough-to-peak ratio for diastolic blood pressure 65% to 80%. In the once-daily dose-response studies, trough-to-peak response of ≤50% were observed at some doses (including 1200 mg), suggesting attenuation of effect at the end of the dosing interval."

PRECAUTIONS, Geriatric Use: The third sentence has been revised to read, "In a study of only patients over the age of 65, *Teveten* at 200 mg twice daily (and increased optionally up to 300 mg twice daily) decreased diastolic blood pressure on average by 3 mmHg (placebo corrected).

ADVERSE REACTIONS, Laboratory Test Findings: A new sentence has been added at the end of this subsection: "Patients were rarely withdrawn from Teveten because of laboratory test results."

ADVERSE REACTIONS, Creatinine, Blood Urea Nitrogen: The second sentence has been revised to read, "Two patients were withdrawn from clinical trials for elevations in serum creatinine and BUN, and three additional patients were withdrawn for increases in serum creatinine."

ADVERSE REACTIONS, Hemoglobin: In the second sentence ' has been replaced by "Two" in the sentence, " Two patients were withdrawn from clinical trials for anemia.

ADVERSE REACTIONS, Neutropenia: The second sentence has been revised to read, "No patient was withdrawn from any clinical trials for neutropenia."

ADVERSE REACTIONS, Thrombocytopenia: In the second sentence, has been replaced by "Four" in the sentence "Four patients receiving Teveten in clinical trials were withdrawn for thrombocytopenia."

ADVERSE REACTIONS, Serum Potassium: In the second sentence, has been replaced with "One patient was" and ' has been replaced with "three" in the sentence, "One patient was withdrawn from clinical trials for hyperkalemia and three for hypokalemia."

DOSAGE AND ADMINISTRATION: The first paragraph has been replaced with the following:

> "The usual recommended starting dose of Tevetan is 600 mg once daily when used as monotherapy in patients who are not volume depleted (See WARNINGS, Hypotension in Volume-and/or Salt-Depleted Patients). Tevetan can be administered once or twice daily

with total daily doses ranging from 400 mg to 800 mg. There is limited experience with doses beyond 800 mg/day.

"If the anti-hypertensive effect measured at trough using once-daily dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response. Achievement of maximum blood pressure reduction in most patients may take 2 to 3 weeks."

In what is now the third paragraph, in the second sentence, "of" has been replaced with "with," to read, "Discontinuation of treatment with eprosartan..."

HOW SUPPLIED: "Rx only" has been added.

Recommendation:
I will prepare an approval letter for this supplement for Dr. Lipicky's signature. This supplement falls under 21 CFR 314.70 (b)(3) Supplements requiring FDA approval before the change is made.

/S/
Kathleen F. Bongiovanni 10-13-98

cc: NDA 20-738/S-001
HFD-110
HF-2/MedWatch
HFD-110/KBongiovanni
HFD-110/SBenton
kb/10/13/98.

K·Borgiovanni
AUG 28 1998

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
LABELING REVIEW

NDA#20,738 AMENDMENT 3
SUBMISSION DATED AUGUST 21, 1998
DRUG NAME: Teveten ® (eprosartan)
MEDICAL REVIEWER: Maryann Gordon, MD /S/ 8-28-98

Introduction
This amendment was submitted by the sponsor to justify their revision of the number of drop outs because of laboratory abnormalities in the eprosartan labeling. The original label was written by the Division using drop outs listed in Table 8.3.A of the eprosartan safety update. The Division at that time believed that the table had been reviewed by the sponsor before they submitted it and that it was correct.

Subsequently, the sponsor has explained why certain patients listed in Table 8.3.A should not be included in the label and, after reviewing their statements, I accept the their explanations and the revised numbers. I am of the opinion that the confusion is strictly the result of poor study monitoring.

In addition to the above, I have reviewed the post approval safety and it includes the following reports:

Post marketing safety
-62 year old male was diagnosed with toxic liver disease, cholestasis and urinary retention. Abnormal laboratory values included elevated liver function tests, increased creatinine, hematuria, and proteinuria Medications included eprosartan for 16 days, hydrochlorothiazide/triamterene, phenoxymethylpenicillin, and ofloxacin

-43 year old male with a history of chronic active hepatitis B and class IV heart failure and drug and alcohol abuse experienced fatigue and greatly elevated liver function tests and total bilirubin. He was taking eprosartan for about 9 months. Drug was discontinued and levels began to decline about 1 month later. Ultrasound showed hepatosplenomegaly and a normal gall bladder. Concomitant medications include digoxin, enalapril, metoprolol, lasix, aspirin, vitamin K.

-55 yo male in Germany developed thrombocytopenia 2 weeks after starting eprosartan. No platelet count was provided. There is a complex medical history which includes Hodgkin's disease and adenocarcinoma with liver metastases. Apparently he had normal platelet count prior to taking eprosartan.

-46 year old male with heart failure had ventricular fibrillation and died during treatment with eprosartan 200 mg for about 48 days. Medical history included anemia, chest pain, diabetes, mitral regurgitation. Other drugs included captopril,

digoxin, isordil, carvedilol, lasix, nitroglycerine.

-2 reports of angioneurotic edema. Both cases resolved with drug discontinuation.

-71 year old male developed decreased urine output after first dose and severe diarrhea, dehydration, and acute renal failure. BUN and creatinine values were elevated. Patient recovered. There is confusion about the actual duration of use of eprosartan. Concomitant medications included enalapril, allopurinol, furosemide and metoprolol. Medical history was significant for cardiovascular and peripheral vascular disease.

Recommendations
I agree with the changes proposed by the sponsor. In addition, I believe that a statement in the labeling warning about possible aggravation of existing liver disease with the use of eprosartan should be considered by the Division.

Withdrawals for abnormal laboratory values

Serum creatine and BUN:
Two patients with increases in serum creatinine and BUN and three with increases in serum creatinine only.

Liver function tests:
Four patients with increases in LFTs

Anemia:
Two patients with anemia

Neutropenia:
No patients with neutropenia

Thrombocytopenia:
Four patients with thrombocytopenia

Hyper- and hypokalemia:
One with hyperkalemia and three with hypokalemia

FEB 3 1998

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: FEB 3 1998

FROM: Albert DeFelice, Ph.D., Team Leader (Pharmacology)
Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Hepatic Clinical Chemistry/Histopathology Profiles in Pre-Clinical Toxicity Tests of Seven NDA "Sartan" Compounds

TO: File - NDAs 20-386, 20-665, [redacted] 20-757, 20-838, and 20-850
Through: Robert Fenichel, M.D., Ph.D., Deputy Director
Division of Cardio-Renal Drug Products, HFD-110

Summary:

Animal toxicity test results of each of the seven approved or pending "sartans" were re-visited by certain of the Division's review pharmacologists (Drs. A. Proakis, J. Koerner, G. Jagadeesh, T. Papoian, and myself) to look, only, for any histologic or clinical chemistry evidence of hepatotoxicity. Data base included a) 14 lifetime rodent studies (mice and rats) done at up to max. tolerated dosages, b) 6 more chronic (6-12 mo.) rodent studies ; c) 5 oral dog studies (4 3 -12 mo. studies; 1 1-mo. study) at doses affording 10-50X human AUC plasma exposure, d) 2 intravenous dog studies (1-day; 30 days) at up to 50X human plasma exposure), and e) 5 oral monkey studies (3 6-12 mo.; 2 1-3 mo.) done at up to 50X human AUC plasma exposure. My scrutiny of losartan (orig. reviewers: Drs Proakis and Jagadeesh) included examining the trajectory of clin. chemistries for individual animals in chronic studies with a serial bleed design.

Despite unblinded review of the data - and foreknowledge that these agents may damage human liver - neither the individual evaluations, nor my overview of them, perceived any concentration or duration-related hepatotoxicity in rodents, dogs, or monkeys - as concluded in the original reviews of these studies. Where individual animal data were available, the occasional 2-4 fold increase in ALT value over basal level was confined to either dog or monkey (not both in a given sartan) and , furthermore, were not accompanied by AST, AP, bilirubin, or liver histology change in that animal. Perhaps compellingly, there was no excess liver histopathology in tumorigenicity assays performed at lifetime exposure of mice and rats at up to maximum tolerated(or otherwise acceptable) dosages of each of the sartans.

A summary of the scope, and duration, of animal toxicity studies which monitored both clinical chemistries and histology follows:

TASOSARTAN :

Chronic oral studies:

52 wk: mouse and rat: No signif incr. in AST, ALT, or AP at up to 100 mg/Kg vs. concurrent control group. Max. exposure vs. human: 30X.

2-yr. rodent tumorigenicity : No excess liver histopathology vs concurrent control in either species at up to approx. Max. Tolerated Dose in either species (ca. 30X human exposure).

13 and 26 week monkey: No clin. chem. or histologic evidence of hepatotoxicity at up to approx. 70X human exposures.

52 wk. monkey: A transient 3-fold increase in one, and a sustained 2-fold in a second , of 4 females at 15 mg/Kg without change in AST, AP, bilirubin, or liver histology. No liver changes at higher dose (45 mg/Kg) in 4 other females and 4 males.

EPROSARTAN :

Chronic oral studies:

13-week mouse: No evidence of hepatotoxicity at up to 2000 mg/Kg.

6-month rat: At 1000 mg/Kg, mean ALT and AST in females are 1.5 X concurrent control. No associated liver histopath.

2-year mice/rat: No histologic evidence of hepatotoxicity at up to approx. max. tolerated dosage.

12- month dog.: At up to 1000 mg/Kg, no clin. chem. or histologic evidence of any hepatotoxicity (dose is 100x dog efficacious dose; affords 10 x human blood levels).

Single iv dose, dog ALT, AST, and AP raised 2-5 fold 3 days post 300 mg/Kg iv. Mild multifocal cholagiitis only liver histopath. Dosage affords 1000X human free drug level.

VALSARTAN:

Chronic oral studies

3-12 mo rat: No clin. chem. (ALT, AST, AP, bilirubin) or histologic evidence of hepatotox. at up to 600 mg/Kg/ 3-mo. (which affords 100 X human free drug AUC) or 200 mg/Kg/year. (which affords 35X human free drug AUC).

3-12 mo. marmoset: No clin. chem. or histologic evidence of hepatotox. at up to 120 mg/Kg/ 12 mo.(ca. 60X human dose). At ≥ 200 mg/Kg/ 3-mo.: 36% incr. in AP; marked lipid vacuolation of liver in 3 animals; 1 animal with mild chronic hepatitis and minimal focal necrosis in liver.

14-day iv,:

Marmoset: No evidence of hepatotoxicity after 60 mg/Kg iv / day / 2 weeks. (dose is estimated to afford ca. 300 X human serum drug levels).

Rat: No evidence of hepatotoxicity after 100 mg/Kg iv / day / 2 weeks. (dose is estimated to afford ca. 500 X human serum drug levels).

TELMISARTAN:

Chronic oral studies:

26-week rat: 2 -fold increase in total bilirubin (but no other clin. chem., or liver histopath.), and 25% decr. in liver wt. at 500 mg/Kg, which affords 200- 300X human free drug AUC exposure. 1 mg/Kg is efficacious dose in this species.

52-week dog: No change in ALT, AST, AP, LDH, or total bilirubin at up to 500 mg/Kg which affords ca. 40X the human AUC exposure to free drug.

Intravenous studies:

4-week ,rat: Liver wt. decreased 10-15% without histopathology.

30-day , dog: At 50 mg/Kg, mean AST, ALT, and LDH in females increased 2, 10, and 2-fold, respectively , vs. baseline, and one male also had 2-fold increase in these enzymes. Liver wts. increased ca. 10-15% in both sexes, with no histopathology. Dosage afforded 52-63X human AUC exposure to free drug. Although exposure was not markedly higher than that achieved in the 1-year oral dog study, liver enzymes were not elevated in the latter.

CANDESARTAN:

Chronic oral studies:

6-mo., rat (10/sex/dose): There was no clin. chem. (including ast, alt, ap, and bilirubin) or histologic evidence of hepatotoxicity at up to 1000 mg/Kg daily in either sex.

52-week, dog(4/sex/dose): There was no clin. chem. (include. aminotransferase and bili.) or histologic evidence of hepatotoxicity at up to 300 mg/Kg daily in either sex.

4-week, monkey (2/sex/dose): At 300 mg/Kg daily, 2-fold incr. in ALT in 1 male and AST in 1 female at 4 -weeks, with no other enzyme, bilirubin , or liver histology change.

LOSARTAN:

Sub-acute and Chronic oral studies:

Rodent:

14 week rodent (15/sex/dose).:
Except for a 40% incr. above control in high-dose males at wk.12, there was no stat. signif. increase in ALT at dosages up to 450 (rat) and 500 (mice) mg/Kg /day/14 weeks. No bilirubinemia or liver histopath. cited. It must be noted that the high dose in this study was lethal to approx. 20% of both sexes of rats

14-week mice: (15/sex/dose). No change in ALT

1-year rat: (30 /sex/dose). No ALT, bilirubin, or liver histopathology. No hemorrhages cited even at high ulcerogenic dosages.

2-year rat tumorigenicity: (30 /sex/dose). : No excess liver histopathology or hemorrhagic deaths cited even at high (ulcerogenic) dosage. Clin. chem. not monitored.

2-year mouse tumorigenicity: (30 /sex/dose).: No serum ALT, bilirubin, hepatic histology, or hemorrhagic deaths cited even at the ulcerogenic high dose.

DOG:

1-mo. dog (4/sex/dose): Tested at up to 125 mg/Kg, affording 50X human plasma Cmax. A transient doubling of ALT in one high-dose dog , but stable AST, bilirubin , and albumin in that dog, and no liver histopathology (his blood level was ca. 50X human ther. level)

3-mo. dog (5/sex/dose): Tested at up to 50 X human Cmax. No change in ALT, AST, bilirubin, or liver histology. Normal ALT values contrast with the positive findings noted below in the 12-month study.

12-mo. dog (8/sex/dose): Losartan was tested at up to 50 X human Cmax. Dosages were 5, 25, and 125 mg/Kg p.o. with 4 dogs/sex/dose being sacrificed at 6-months and the remainder continuing on treatment for an additional 6 months.

The trajectory of serum ALT values, including that of 2 dogs sacrificed, as scheduled, at 27 weeks, is shown in Sponsor's table :

TABLE 3.2.8.1
INDIVIDUAL SERUM ALT (U/L) VALUES. STUDY #90-028-0

Dose mg/kg/day	Pretest -1 week	Drug week					
		4	12	17	25	39	51
25/Male	28	34	73*	83*	99*	-	-
125/Female	36	41	46	49*	167*	86*	199*
125/Female	27	88*	91*	25	37	-	-
125/Male	31	26	43	32	32	49*	46*

* Values outside 95% limits for 3 year control values
- = Sacrificed at interim necropsy

In the course of the study, there were increases in serum ALT values in 4 treated dogs: one mid-dose male dog, one high-dose male, and two high-dose female dogs. The magnitude of the ALT elevation is not obviously dose or time dependent, and is stated as not involving any hepatic histopathology. Positive ALT findings contrast with the absence of findings at comparable intervals and dosages in the 3-mo. study. Although elevations were observed within 4 to 12 weeks in 2 of the 4 presenting dogs of this 1-year study, it is noted that none of the dogs in the 3-month study had elevated ALT levels.

Intravenous studies:

16-day rat (15/sex/dose): At up to 9 mg/Kg/day i.v., no difference in mean ALT or AST vs. concurrent control, or excess liver histopathology.

17 day dog (4/sex/dose): At up to 9 mg/Kg/day i.v., no difference in mean ALT or AST vs. concurrent control, or excess liver histopathology.

IRBESARTAN:

Chronic oral studies:

26-week rat: At up to 1000 mg/Kg (300-1000X efficacious dose), mean serum bilirubin ca. 50% greater than concurrent control at wk. 13 but not 26. No ALT rise, or excess liver histopathology cited.

2 -year rat: At 2000 mg/Kg daily in females , AP, ALT and AST were elevated, but no excess liver histopathology even at this maximum tolerated dose.

2 -year mouse: No liver histopathology at up to 1000 mg/Kg, an approx. maximum tolerated dosage. (clin. chem. not monitored).

1-year monkey: At up to 500 mg/Kg daily (500 - 1500 X efficacious dose), no clin. chem. or histologic evidence of hepatotoxicity.

cc:
Orig.
HFD-110
HFD-110/Project Manager
HFD-110/ADeFelice

NDA 20-738

S-001

Teveten™ Tablets

(Eprosartan Mesylate; SK&F 108566-J)

DEBARMENT STATEMENT

SMITHKLINE BEECHAM PHARMACEUTICALS HEREBY CERTIFIES THAT SAID APPLICANT DID NOT USE IN ANY CAPACITY THE SERVICES OF ANY PERSON DEBARRED UNDER SUBSECTION (A) OR (B) [SECTION 306(A) OR (B) OF THE ACT], IN CONNECTION WITH THE NEW DRUG APPLICATION FOR TEVETEN™ (EPROSARTAN MESYLATE) TABLETS. THE APPLICANT FURTHER CERTIFIES THAT NO SUCH PERSON DEBARRED BY THE FOOD AND DRUG ADMINISTRATION WILL BE USED IN ANY CAPACITY IN FUTURE INVESTIGATIONS INVOLVING THIS DRUG PRODUCT, AT SUCH TIME AS SAID DEBARMENT BECOMES KNOWN TO THE SPONSOR.